# Urticaria and Angiodema:
## An Update

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**Conflict of Interest Disclosures:**

**Jonathan A. Bernstein, MD FACAAI, FAAAAI**

Employment: University of Cincinnati and Bernstein Allergy Group and Clinical Research
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**Learning Objectives**

Upon completion of this session, participants should be able to:

- Discuss the differential diagnosis for urticaria and angioedema
- Properly assess patients with urticaria and angioedema
- Summarize the current therapeutic options for urticaria and angioedema

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## Ûr´tĭ-kâr´ē-ə

- Urticaria is characterized by intense itching welts caused by allergic reactions to internal and external agents
- From the Latin word urtīca which means "nettle"
- "Nettle" refers to any plant from the genus *Urtica.* These plants have toothed leaves covered with hairs that secrete a stinging fluid which effects the skin on contact
- Nettles were used during ancient times as a treatment for paralysis

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## Features of Urticaria

- Raised, pink/erythematous skin lesions that are markedly pruritic; lesions range from a few millimeters to several centimeters in size and may coalesce
- Evanescent; old lesions go and new ones come over 24 hours leaving no scarring
- Generally worsened by scratching
- Any area of the body may be involved; most common areas are the perioral and periorbital regions, tongue, genitalia and extremities

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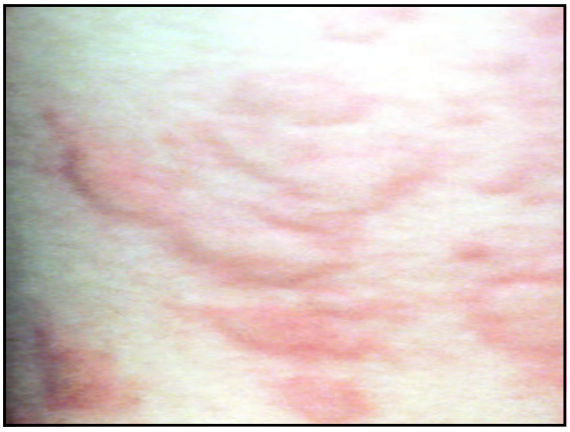

## Triple Response of Lewis

- Erythema – due to capillary and venule dilatation
- Flare – due to an axonal reflex leading to further erythema
- Edema – due to increased capillary permeability; extravasation of fluid from the blood vessel
- Pruritis – neuronal reflex mechanism

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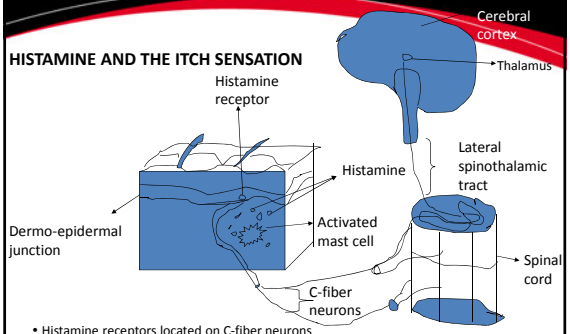
## HISTAMINE AND THE ITCH SENSATION




- Histamine receptors located on C-fiber neurons
- Histamine binding triggers an itch impulse

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## Histopathology of Chronic Urticaria

- Predominant cell types are lymphocytes that express HLA-DR antigen arranged perivascularly
- May see increased number of mast cells
- No evidence of vascular damage, nuclear debris or red cell extravasation
- Some forms of urticaria exhibit neutrophils within capillary and post-capillary venular walls without structural damage; possible intermediate form between “ordinary” urticaria and urticarial vasculitis

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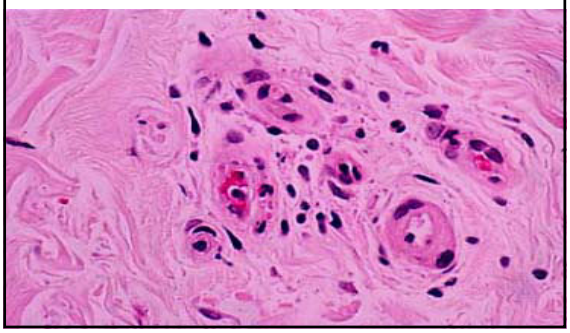
**Histology: Dermal edema and a mild perivascular infiltrate of lymphocytes, eosinophils and neutrophils**



## Prevalence of Urticaria

- Estimated to occur in 15-23% of the U.S. population
- Up to 40% of patients who have chronic urticaria longer than six months will still have urticaria 10 years later
- Approximately 40% of patients with chronic urticaria have angioedema

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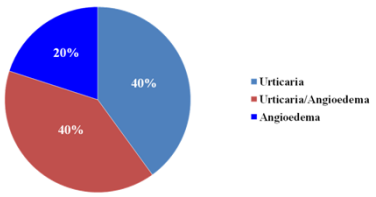
## Prevalence of Urticaria With and Without Angioedema

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## Urticaria

- Acute urticaria refers to hives lasting less than six weeks; in approximately 15-20% of cases an inciting cause can be identified
- Chronic urticaria refers to hives lasting longer than 6-8 weeks; identification of a cause is less than 5%

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## Classification of Chronic Urticaria

- Chronic ***idiopathic*** urticaria (most common cause)
- Physical urticarias
  - Symptomatic dermatographism
  - Delayed pressure urticaria
  - Cold urticaria
  - Aquagenic urticaria
  - Solar urticaria
  - Cholinergic urticaria
  - Vibratory angioedema and urticaria
- Urticarial vasculitis (<1% of urticaria)

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## Differential Diagnosis: Immunologic Causes More Often Responsible for Acute Urticaria

- Foods
- Many drugs
- Insect stings
- Transfusion reactions
- Contactants/Inhalants (rare)

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## Differential Diagnosis: Non-Immunologic Causes More Often Responsible for Chronic Urticaria

- Physical hives (i.e., dermatographism, pressure, solar, cold…)
- Hereditary (i.e., cold, heat, vibratory, porphyria, C3b inactivator deficiency…)
- Vasculitis
- Neoplasms
- Infections
- Endocrine
- Drugs (i.e., aspirin/NSAIDs-exacerbate hives in up to 30% of cases)
- Psychologic? More a myth than fact

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## Features of Physical Urticaria

| Type | Age (yrs) | Clinical Features | Angio-edema | Diagnostic Test |
|---|---|---|---|---|
| Dermatographism | 20-50 | Linear lesions | No | Light stroking of skin; + transfer factor |
| Cold (primary vs. secondary) | 10-40 | Itchy, pale lesions (5% with cryos) | Yes | 5-10 minute ice-cube test; + transfer factor |
| Cholinergic (heat bumps) | 10-50 | Itchy, monomorphic pale or pink lesions | Yes | Exercise or hot shower; + transfer factor |
| Pressure | 20-50 | Large painful or itchy lesions | No | Dermographometer; application of pressure to skin |
| Solar | 20-50 | Itchy pale or red swelling | Yes | Irradiation by a solar simulator;+ transfer factor |

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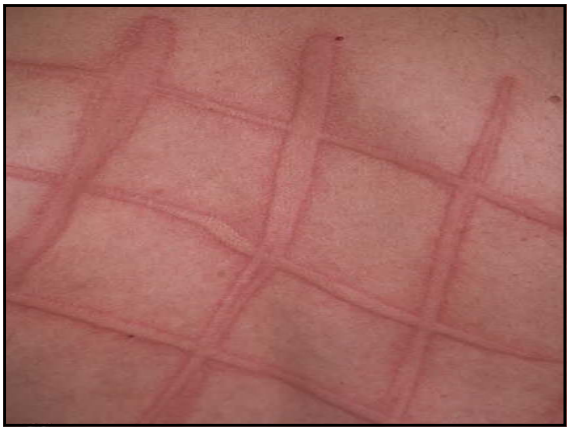

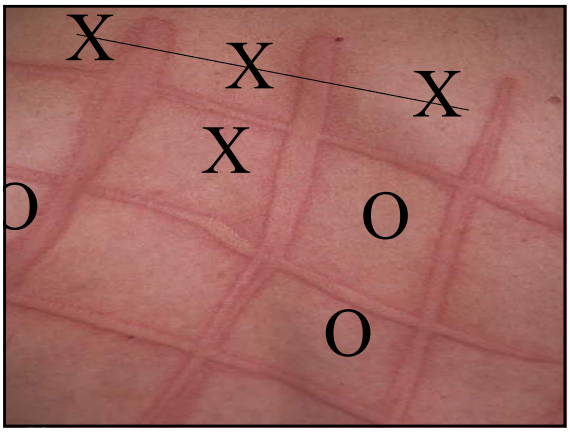
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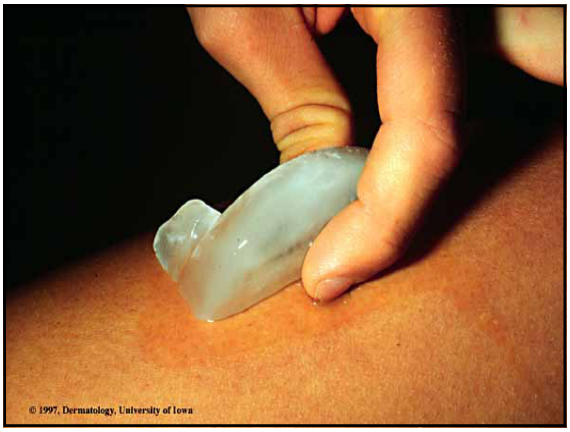
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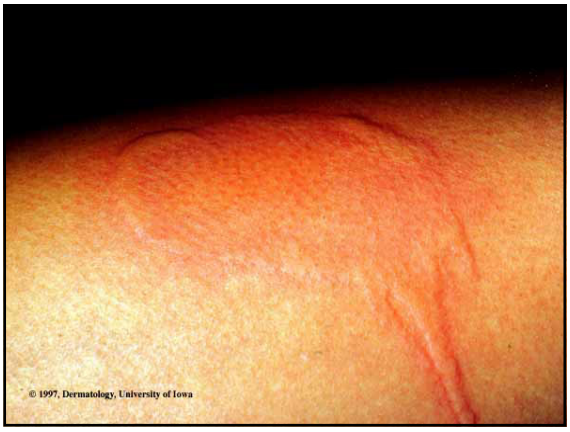
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## Familial Cold Urticaria (aka. Familial Cold Autoinflammatory Syndrome)

- Autosomal dominant
- Characterized by episodic urticaria, arthralgias, fever and conjunctivitis after exposure to cold
- Same genetic locus on chromosome 1q44 as Muckle-Wells syndrome (an autosomal dominant periodic fever syndrome associated with hives and sensorineural hearing loss)
- Cryopyrin gene preferentially expressed in families with this disorder; significant homology to the Nod2 gene implicated in Crohn's disease

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Hoffman HM, et.al. Nat Genet 2001; 29:301-5.

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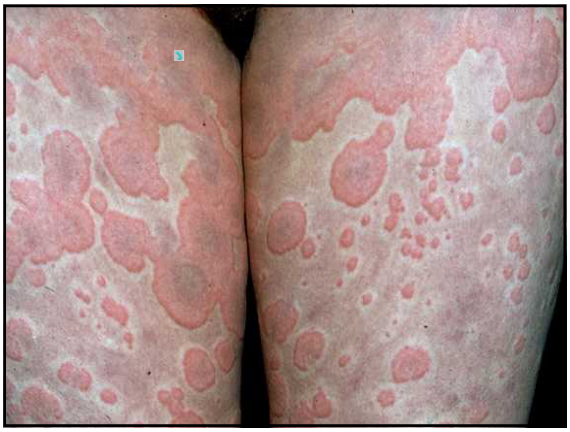

## Urticarial Vasculitis: Features That Differentiate It From CIU

| Feature | Chronic urticaria | Urticarial vasculitis |
|---|---|---|
| Wheal duration | <24 hr | >24 hr (not always true) |
| Purpura/pain/hyper-pigmentation | No | Yes |
| Systemic signs | Usually none | Yes |
| Laboratory findings | Usually normal | Increased WSR, Acute Phase Reactants; Decreased C3/C4 |
| Leukocytoclasia or extravasation of RBCs | No | Yes |
| Response to antihistamines | Yes | Sometimes |

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## Chronic Urticaria and Malignancy

**Lindelof B, et.al. Br J Dermatol 1990;123:453-6**

- 1,155 cases of CIU were identified and reviewed
- A search of the Swedish Cancer Registry for malignancies in this population was conducted for the years 1958-84
- The expected number of malignancies was calculated based on age and sex-standardized incidence data
- Malignancy was diagnosed in 36 CIU patients from this population which was less than the expected calculated number of malignancies of 41
- *Conclusion*: CIU not statistically associated with malignancy

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## Chronic Urticaria and Malignancy

- In general, malignancy associated with chronic urticaria is rare but there is probably a link
- Case reports-
  - Schnitzler's syndrome: chronic urticaria associated with IgM monoclonal gammopathy
  - Chronic myelogenous leukemia
  - Other lymphoreticular malignancies

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## Chronic Urticaria and Infection: Hepatitis

- Hepatitis A – case reports of acute hives only
- Hepatitis B – 2/85 subjects with hives had positive HBsAg (Vaida GA, et.al. JACI 1983;72:193-8.)
- Hepatitis C and G – 0/110 patients with chronic urticaria had HCV RNA; 2 control subjects and 2 hive subjects had circulating HGV RNA without HCV and normal LFTs (Cribier BJ, et.al. Arch Dermatol 1999; 135:1335-9)

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## Chronic Urticaria and Infection: Parasitism

- Anisakis simplex is a cephalopodes parasite
- Ingestion of larvae can cause urticaria, angioedema, erythema, bronchospasm and anaphylaxis
- Specific IgE has been demonstrated in subjects after chronic ingestion (Daschner A, et.al. JACI 2000;105:176-81.)
- Ongoing debate whether this is a parasitic infection vs. food allergy

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## Chronic Urticaria and Infection: Helicobacter pylori

- 42 patients in Italy with CIU were evaluated for H.pylori by [13C] urea breath test; 55% were infected and 88% showed total or partial improvement of their hives after triple therapy with amoxicillin, clarithromycin and lansoprazole (Di Campli C, et.al. Dig Dis Sci 1998;43:1226-9)
- 26/100 German patients with CIU evaluated in a dermatology clinic had H. pylori associated gastritis; 67% had disappearance & 24% had partial improvement after treatment; 50% of untreated patients had spontaneous remission of their hives after 12 weeks (Wedi B, et.al. Int Arch Allergy Immunolo 1998;116:288-94)
- Similar findings in Japan (Sakurane M, et.al. J Dermatol 2002; 29:23-7.)

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## Chronic Urticaria and Autoantibodies

- Thyroid autoantibodies (Hashimoto's > Graves' disease)
- Uncertain whether identification of autoantibodies represent a parallel abnormality which reflects an underlying autoimmune process or is functionally related to chronic urticaria

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## Evaluation of Autoantibodies In CIU

- Sera from 25 patients with CIU were tested for autoantibodies and compared to 75 controls
- One patient had inflammatory bowel disease and one had multiple myeloma
- Antibodies to thyroid peroxidase and RF were increased in the CIU population but no other autoantibodies were found
- In general, non-specific autoimmunity was not identified in the CIU population

Ryhal B, et.al. J Investig Allergol Clin Immunol 2001;11:16-20.

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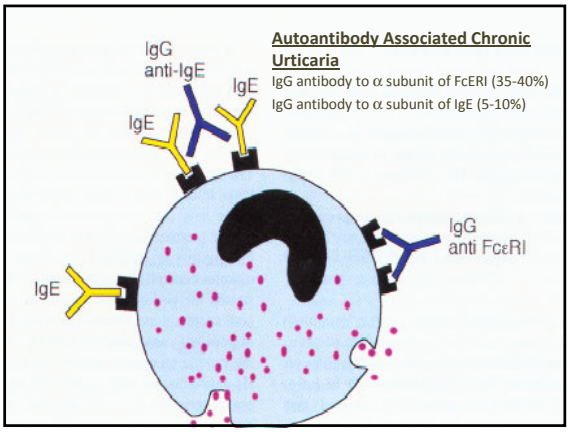
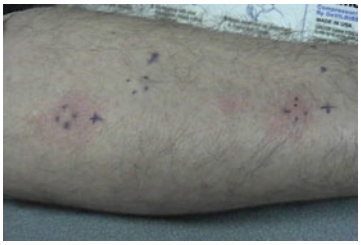



**Autoantibody Associated Chronic Urticaria**

IgG antibody to α subunit of FcERI (35-40%)

IgG antibody to α subunit of IgE (5-10%)

## Autologous Serum Skin Test



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## Autoantibody Induced Chronic Urticaria

**Hide M, et.al. NEJM 1993;328:1599-604**

- 26 patients with CIU were skin tested intradermally to autologous serum (0.05 cc) which elicited a wheal/flare response suggesting an autoantibody to FcεRI α subunit
- Incubation of basophils isolated from a non-atopic donor (low serum IgE) with serum from these patients demonstrated an increase in histamine release
- Passive sensitization of basophils with myeloma IgE and pretreatment with IgG fractions containing sFcεRIα abolished histamine release; basophils, treated with lactic acid to dissociate IgE, and then passively sensitized to serum from patients with autoantibodies to FcεRI, resulted in enhanced histamine release
- ***Conclusion: Proposed mechanism of autoimmune induced chronic urticaria is due to cross-linking of IgE receptors by an IgG antibody to FcεRIα resulting in release of bioactive mediators such as histamine***

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## Are Autoantibodies to FcεRI α Functionally Related to Urticaria?: A Case Report

- 45 y/o AAF with a 20 year history of CIU refractory to $H_1$- and $H_2$-antagonists and other anti-inflammatory agents but controlled on daily prednisone (35 mg) for over 13 years resulting in 100 # weight gain among other side effects
- Intracutaneous testing to autologous serum revealed an 8 X 10 mm wheal/flare reaction c/w autoantibodies to FcεRI α
- Treatment with IV cyclophosphamide was initiated to eradicate autoantibody producing B-lymphocyte clones; this approach previously successful in other autoantibody-mediated disorders such as Type II acquired angioedema and Factor VIII deficiency
- The total dose of CTX administered represented 20% of the standard dose administered for systemic chemotherapy
- After seven months of treatment, there was complete clinical remission of hives and prednisone was discontinued
- Repeat intracutaneous testing to autologous serum was negative
- The patient remained hive free 5 years after treatment

Department of Internal Medicine — Bernstein JA, et.al. Ann Allergy (2002). — University of Cincinnati

## Chronic Urticaria: The Evaluation

- History/Physical Examination
- Evidence of dermatographism or other forms of physical hives?
- Initial laboratory testing should be limited (CBC with differential, WSR, TSH, LFT's, U/A)
- Refractory cases: C4, thyroid antibodies, H. pylori antibodies, hepatitis screen
- Atypical non-evanescent hives: skin Bx (H&E; IF)
- Skin testing to autologous serum?
- **ALLERGEN SKIN TESTING IS NOT INDICATED IN THE PRIMARY EVALUATION OF HIVES!**

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## Treatment Rationale

- Use an algorithmic approach to identify the medication or combination of medications that completely prevent the occurrence of hives
- Should begin with agents that have fewer side effects as treatment is often prolonged
- Each treatment trial should be at least 2 weeks
- For severe cases, oral corticosteroids are sometimes required to initially control hives followed by slow taper to determine the effectiveness of primary treatment(s)

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## Chronic Urticaria: Available Treatments

| Drug Class | Mechanism |
|---|---|
| $H_1$-receptor antagonist: Class I – sedating (hydroxyzine, diphenhydramine, cyproheptadine) Class II – non- or low-sedating (fexofenadine, loratadine, desloratadine, cetirizine) | Blocks histamine binding to $H_1$ receptors; some block other receptors (serotonin); others have mast cell stabilizing properties |
| $H_2$-receptor antagonist: cimetidine, ranitidine, famotidine | Blocks histamine binding to $H_2$ receptors |
| $H_1$- and $H_2$- receptor antagonists: Doxepin | Blocks $H_1$, $H_2$ and muscarinic receptors |
| Leukotriene modifying agents: montelukast, zafirlukast, zileuton | Blocks LTC4/D4 receptors or 5-lipoxygenase |
| Mast-cell stabilizing agents: oral albuterol, azatadine | Attenuates histamine release from mast cells and basophils |
| Corticosteroids: prednisone, methylprednisolone | Attenuates inflammation; blocks cytokine production? |

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## Treatment of Chronic Urticaria

- Therapy with antihistamines work best for most patients with acute-types of short-lasting urticaria
- Combination therapy should be attempted if H1 antagonists do not suffice (30% of cases)
- Steroids and other immunosuppressants should be reserved for severe urticaria associated with angioedema of oropharnyx or other systemic signs, moderate to severe drug reactions, urticarial vasculitis, and refractory cases of CIU

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## Leukotriene Modifying Agents

- Intradermal injection of leukotrienes:
  - LTC4, LTD4, LTE4 – vascular effects only with wheal lasting 2 hours and flare lasting 6 hours
  - LTB4 – transient wheal and flare followed by neutrophil infiltration into the dermis within 4 hours

  Maxwell DL *et al J Allergy Clin Immunol* 1990; 86: 759-65
- Leukocyte suspensions released twice as much sulfidoleukotrienes *in vitro* with serum from patients with positive autologous serum skin test compared to normals

  Wedi B *et al J Allergy Clin Immunol* 2000; 105: 552-60
- Patients with positive autologous serum skin test and CIU benefitted from zafirlukast 20 mg bid when added to cetirizine 10 mg (physician visual analogue score – VAS)

  Bagentose SE *et al. J Allergy Clin Immunol* 2004; 113: 134-40

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## Leukotriene Modifiers

- Montelukast effective in group of patients in SB, PC cross-over
  - Cetirizine used for rescue
  - 9/11 patients with positive autologous skin test converted to negative after montelukast therapy
  - Best response seen in patients sensitive to aspirin

  Erbagci Z *J Allergy Clin Immunol* 2002; 110: 484-8
- No significant benefit in adding montelukast to desloratadine above desloratadine itself in CIU

  Di Lorenzo G *et al. J Allergy Clin Immunol* 2004; 114: 619-25

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## Chronic Urticaria: Treatments for Specific Considerations

- Calcium channel blockers + azatadine in pressure-induced urticaria
- Dapsone or colchicine in patients with neutrophilic infiltrates on skin biopsy
- L-thyroxine in patients with thyroid autoantibodies
- Case studies: stanazolol (works by increasing serum proteases), heparin, coumadin, cyclosporin, gold, plaquenil, methotrexate
- Autoantibody associated CU: CTX, plasmapheresis, IVIG, omalizumab

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## Cyclosporin

- Inhibits IL-2, IL-3, IL-4, IFN–gamma, GM-CSF, and TNF-alpha production
- Inhibits NF-AT, nuclear factor kappa beta (NF-KB), and PU box
  Maraoka K, *et al. J Clin Invest* 1996; 97: 2433-9
- Prevents GVHD
- Treatment psoriasis, RA, Crohn's, Behcet's, aplastic anemia, polymyositis, dermatomyositis
  Faulds D *et al Drugs* 1993; 45: 953-1040
- Low dose (3 mg/kg) cyclosporine (CsA) effective in treating patients with CIU in 13/19 (full remission) and 6/19 (significant relief) compared to controls over three months
  Toubi E *et al Allergy* 1997; 52: 312-6
- DB, PC trial with 4mg/kg CsA revealed improvement in daily urticaria score (42 points max) by 12.7 (vs 2.3 in placebo)
  - Histamine release decreased from 36% to 5% (p<0.0001)
  - Autologous skin test also reduced in responders
    Grattan CE *et al. Br J Dermatol* 2000; 143: 365-72

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## Auto-Antibody Associated urticaria/angioedema

- Design:
  - 4 week wash out with placebo
  - Omalizumab x 16 weeks
    - Q2 weeks or Q4 weeks
    - IgE < 30 IU/mL → 150mg Q4 weeks
  - Single-blind to treatment sequence
- Measures:
  - Urticarial symptom diary
  - Dermatology Life Quality Index
  - Pruritus score
  - Urticaria Activity Score
  - Pre- and Post-treatment basophil histamine release and autologous serum skin test
- Rescue medication:
  - Hydroxyzine 25-50mg QID prn
  - Oral corticosteroid at discretion of PI

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Kaplan et al. JACI. 2008; 122(3)

## Proof of Concept Study: Is Omalizumab Effective For Treatment of Urticaria/Angioedema

**TABLE II.** Patient characteristics

| Patient no. | Age (y) | Sex | Duration of symptoms (continuous) | Total serum IgE (IU/mL) | Thyroid antibodies | Baseline UAS (0-9) |
|---|---|---|---|---|---|---|
| 1 | [redacted] | [redacted] | [redacted] | [redacted] | Negative | [redacted] |
| 2 | | | | | (*) Negative | |
| 3 | | | | | (+) Antiperoxidase (824) | |
| 4 | | | | | Negative | |
| 5 | | | | | Negative | |
| 6 | | | | | (+) Antiperoxidase (54) | |
| 7 | | | | | Negative | |
| 8 | | | | | (+) Antiperoxidase (250) | |
| 9 | | | | | (+) Antiperoxidase (50) | |
| 10 | | | | | (+) Antithyroglobulin (41) | |
| 11 | | | | | Negative | |
| 12 | | | | | Negative | |

F, Female; M, male.
(*) History of Hashimoto thyroiditis, although autoantibodies were negative.
(+) Positive, titer shown in parentheses.

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Kaplan et al. JACI. 2008; 122(3)

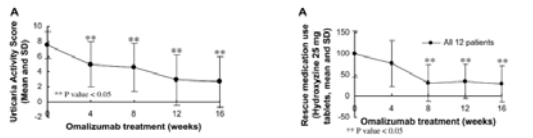
## Autoantibody Associated Urticaria/Angioedema

**TABLE I.** Scoring system for urticaria severity

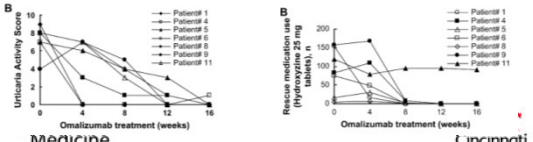
| Score | Pruritus severity | No. of hives | Size of largest hive (cm) | Interference with sleep | Interference with daily activities | Erythema severity |
|---|---|---|---|---|---|---|
| 0 | None | None | None | None | None | None |
| 1 | Mild, minimal awareness, easily tolerated | 1-6 | <1.25 | Mild, not troublesome, adequate sleep | Mild, not troublesome, little effect on activity | Slight |
| 2 | Moderate, definite awareness, bothersome but tolerable | 7-12 | 1.25-2.5 | Moderate, awoke occasionally, average sleep | Moderate, some interference with activity | Moderate |
| 3 | Severe, difficult totolerate | >12 | >2.5 | Severe, substantial interference with sleep, poor sleep | Severe, daily activities substantially or completely curtailed | Significant |

Kaplan et al. JACI. 2008; 122(3)

## Results



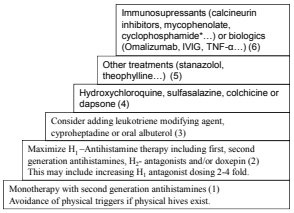

All patients




Patients with complete response

Kaplan et al. JACI. 2008; 122(3)

## Proposed Treatment Algorithm for Chronic Urticaria




**NOTE: "Step-down" in treatment is appropriate at any step described below, once consistent control of urticaria/angioedema is achieved**
Begin treatment at step appropriate for patient's level of severity and previous treatment history
At each level of the step-approach, medication(s) should be assessed for patient tolerance and efficacy or discontinuation to avoid unnecessary polypharmacy.
*For refractory cases with antibodies to FcER1α subunit

## Natural Course/Prognosis of Chronic Urticaria

**Kozel MM, et.al. J Am Acad Dermatol 2001;45:387-91**

- 220 adults with chronic urticaria were followed prospectively for 1-3 years at the University of Amsterdam
- After one year, 35% were free of all symptoms and 30% had decreased symptoms
- 47% of patients with CIU had spontaneous remission over 3 years compared to only 16% who had a component of physical urticaria
- ***Conclusion: Prognosis for spontaneous remission of chronic urticaria is reasonable with the exception of the subgroup with a physical component***

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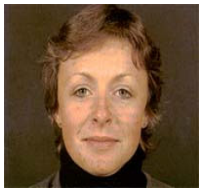
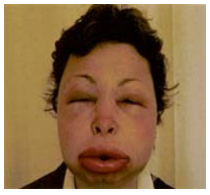
"I must say, Mr. Jennings, you have the worst case of Hives I've ever seen."





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## Hereditary Angioedema (HAE)

- Recurrent localized, non-inflammatory, non-pitting edema of the skin or mucosa (eg, pharynx, larynx, gastrointestinal tract)
- Caused by deficiency in the function of complement component 1 inhibitor (C1INH)
- Autosomal dominant inheritance
  - Type I: lack of expression from one allele (~85%)
  - Type II: expression of a dysfunctional protein from one allele (~15%)
  - Type III: C1 inhibitor normal (enhanced plasma factor XII activity)
- Prevalence of HAE
  - Unknown (orphan disease)
  - Range of 1 per 10,000–50,000[1]
  - Approximate number of cases in U.S. is 2,000–6,000

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Nzeako UC, et al. *Arch Intern Med.* 2001;161:2417–2429.

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## Age at Onset of Hereditary Angioedema (HAE)

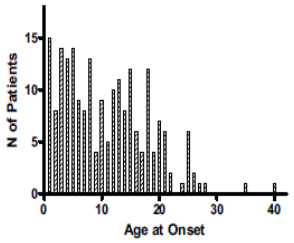


**Figure 1** Age at onset of the clinical symptoms in 209 patients with hereditary angioedema due to C1 inhibitor deficiency.

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Bork K, et al. *Am J Med.* 2006;119:267–274.

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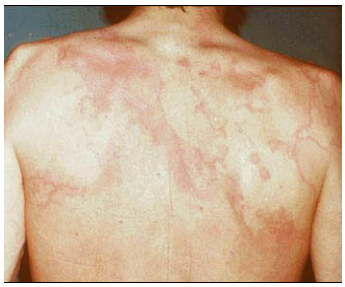
## Erythema Marginatum



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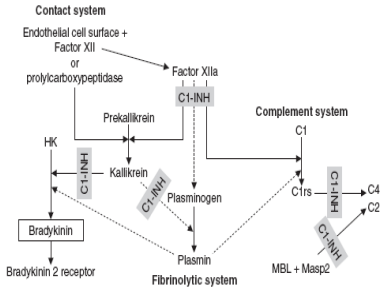
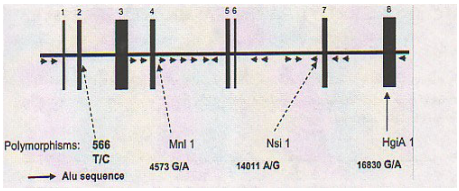
## Biologic Role of C1 Inhibitor




Bernstein JA. *Ann Allergy Asthma Immunol*. 2008;100(suppl 2):S41-S46.

## C1INH Gene and Mutation Sites

- Patients may present without a family history because up to 25% of cases are secondary to a genetic mutation of the C1INH gene




Located on chromosome 11, consists of 8 exons and 7 introns and is approximately 1.7 x $10^4$ base pairs in length.

## C1INH and Complement Levels in Angioedema

| | C1INH antigen | C1INH function | C4 | C2 | C1q | Auto-antibody |
|---|---|---|---|---|---|---|
| **HAE Type I** | ↓ | ↓ | ↓ | ↓ | NI | Absent |
| **HAE Type II** | NI or ↑ | ↓ | ↓ | ↓ | NI | Absent |
| **HAE Type III** | NI | NI | NI | NI | NI | Absent |
| **Acquired Angioedema** | NI or ↓ | ↓ | ↓ | ↓ | ↓ | Present |
| **ACE Induced Angioedema** | NI | NI | NI | NI | NI | Absent |
| **Idiopathic** | NI | NI | NI | NI | NI | Absent |

NI = normal

Adapted from Zuraw BL, Christiansen SC. *Allergy Asthma Proc*. 2009;30:487–492.

## Types of Acquired C1 Inhibitor Deficiency

- Associated with underlying disease
  - Type I: Primarily associated with lymphoproliferative diseases or other autoimmune and neoplastic disorders
  - Type II: Associated with C1 inhibitor autoantibodies

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## Long-term HAE prophylaxis

| Class | Drug name (generic, trade) | Adult dosage (usual, range) | Pediatric dosage (usual, range) | FDA approved/ HAE indication | Side effects |
|---|---|---|---|---|---|
| 17 α-alkylated androgens | | | | | |
| | Danazol (Danocrine) | 200 mg/day, (100mg/q3days-600 mg/day) | 50 mg/day (50 mg/week – 200 mg/day) | Yes / Yes | **Common:** weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities and increase in liver enzymes, hypertension, alterations in lipid profile; **Unusual:** Decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis and hepatocellular adenoma |
| | Stanozolol (Winstrol) | 2 mg/day, (1 mg/q3days – 6 mg/day) | 0.5 mg/day (0.5 mg/week – 2 mg/day) | Yes / Yes | |
| | Oxandralone (Oxandrin) | 10 mg/day (2.5 mg/q3days – 20 mg/day) | 0.1 mg/kg/day (2.5 mg/week – 7.5 mg/day) | Yes / No | |
| | Methyltestosterone (Android) | Men only 10 mg/day 5 mg/q3days – 30 mg/day) | Not recommended for children | Yes / No | |
| | | | | | |
| Antifibrinolytics | | | | | |
| | Epsilon Aminocaproic acid (Amicar) | 2 gm TID (1 gm BID – 4 gm TID) | .05 gm/kg BID (.025 gm/kg BID - .1 gm/kg BID) | Yes / No | **Common:** nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes **Unusual:** enhanced thrombosis |
| | Tranexamic acid (Cyklocapron) | 1 gm BID (0.25 gm BID – 1.5 gm BID) | 20 mg/kg BID (10 mg/kg BID – 25 mg/kg TID) | Yes / No | |

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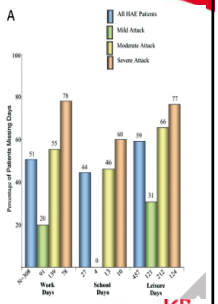
## HAE associated with significant disease burden

- Leads to missed days from school and work
- Increased direct and indirect health care costs
- Decreased quality of life

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## Novel Treatments For HAE

| Drug name (generic, trade) | FDA Indications | Dosage | Mechanism | Anticipated Potential Side Effects |
|---|---|---|---|---|
| Plasma-derived C1 INH (Cinryze; ViroPharma | long-term prophylaxis | 1000 U intravenous | Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin | **Rare:** risk of anaphylaxis Theoretical: transmission of infectious agent |
| Plasma-derived C1 INH (Berinert-P, CSL Behring) | acute attacks, | 20 U per kg intravenous | Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin | **Rare:** risk of anaphylaxis Theoretical: transmission of infectious agent |
| Recombinant-human C1 INH (Rhucin, Pharming) | acute attacks, (potential) | 50-100 U per kg Intravenous | Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin | **Uncommon:** risk of anaphylaxis |
| DX-88 (Ecallantide, Dyax) | acute attacks | 30 mg subcutaneous | Inhibits plasma kallikrein | **Common:** prolonged PTT **Uncommon:** anti-drug antibodies, risk of anaphylaxis |
| HOE-140 (Icatibant, Shire) | acute attacks (potential) | 30 mg subcutaneous | Bradykinin B2 receptor antagonist | **Common:** discomfort at injection site |

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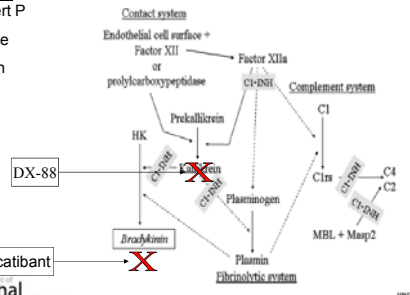
## HAE: Investigational Drugs

C1-INH:
Berinert P
Cinryze
Rhucin

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(Bernstein 2008)

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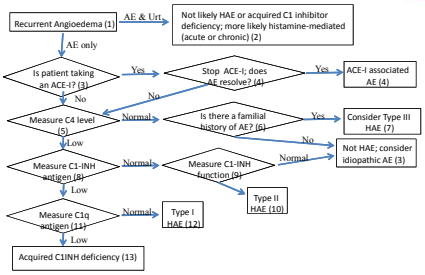
## Figure 1: Recurrent Angioedema Diagnostic Algorithm

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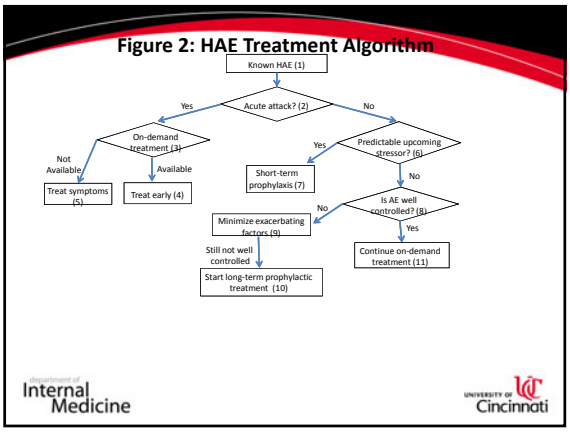
Figure 2: HAE Treatment Algorithm
Known HAE (1)
Acute attack? (2)
Yes
No
On-demand treatment (3)
Not Available
Available
Treat symptoms (5)
Treat early (4)
Predictable upcoming stressor? (6)
Yes
No
Short-term prophylaxis (7)
Is AE well controlled? (8)
No
Yes
Minimize exacerbating factors (9)
Still not well controlled
Start long-term prophylactic treatment (10)
Continue on-demand treatment (11)
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